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Abstract: Asthma and allergy incidence continue to increase globally. We have made significant strides in treating disease, but it is becoming more apparent that we need to advance our knowledge into the origins of asthmatic disease. Much recent work has indicated that microbiome composition influences immune regulation and that multiple health care factors have driven a loss in microbiome diversity in modern human populations. Evidence is growing of microbiota-driven influences on immune development, asthma susceptibility, and asthma pathogenesis. The focus of this review is to highlight the strides the field has made in characterizing the constituents of the human gastrointestinal microbiota, such as Helicobacter pylori, other members of the neonatal intestinal microbiota, and microbial peptides and metabolites that influence host immunity and immune response to allergens. As we delve further into this field of research, the goal will be to find actionable and clinical interventions to identify at-risk populations earlier to prevent disease onset. Manipulation of the host microbial community during infancy might be an especially promising approach.

DOI: https://doi.org/10.1016/j.jaci.2019.10.022

The role of the changing human microbiome in the asthma pandemic

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Keywords
Asthma, allergy, microbiome, Helicobacter pylori

Abbreviations
H. pylori – Helicobacter pylori
Tregs – T regulatory cells
pTregs – peripherally induced T regulatory cells
IBD – Inflammatory bowel disease
DCs – Dendritic cells
GI – Gastrointestinal
EAE – experimental autoimmune encephalomyelitis
GERD – Gastro-esophageal Reflux Disease
SFB – Segmented Filamentous Bacteria
SPF – Select Pathogen Free

Abstract
Asthma and allergy incidence continue to increase globally. We have made significant strides in treating disease, but it is becoming more apparent that we need to advance our knowledge into the origins of asthmatic disease. The evidence of microbiota-driven influences on immune development, asthma susceptibility, and asthma pathogenesis is mounting. The focus of this review is to highlight the strides the field has made in characterizing the constituents of the human gastrointestinal microbiota such as *Helicobacter pylori*, other members of the neonatal intestinal microbiota, and microbial peptides and metabolites that influence host immunity and immune response to allergens. As we further delve into this field of research, the goal will be to find actionable and clinical interventions to identify at-risk populations earlier to prevent disease onset. Manipulation of the host microbial community during infancy may be an especially promising approach.

1. Introduction

Asthma is a chronic inflammatory condition of the lungs that occurs worldwide. Asthmatic symptoms result from airway obstruction due to inflammatory responses to certain triggers, most commonly environmental antigens; multiple cell types and immunological mediators are involved in the pathological processes.[1] It is estimated that more than 300 million people suffer from asthma, with a burden that has increased substantially over the past several decades.[1] Several risk factors have been implicated in asthma susceptibility including host genetics, specific environmental exposures, obesity, and respiratory infections during early life. Attention is now turning to the role of the human microbiome in asthma pathogenesis and protection. The microbiome, a community of organisms including bacteria, archaea, fungi and viruses that live in and on us is now recognized as an important contributor of host homeostasis via physiological, immunological, and metabolic regulation. With improved analytical tools, there has been increasing focus on elucidating the mechanisms by which the constituent microbiota impacts both homeostasis and disease susceptibility. An important frontier is to identify potential therapies to improve human health, prevent the onset of microbiota related diseases, and to identify appropriate therapies. Although these topics are now being studied in relation to obesity, diabetes, inflammatory bowel disease (IBD), and neoplasia, in this review we will focus on asthma and related allergic disorders. We will consider the overall biology of the microbiome, its role in immunological development, and how perturbations are affecting the asthmatic diathesis. Finally, we will consider how the emerging knowledge can be harnessed for improved prevention and therapies

2. Biological characteristics of the human microbiome.

Understanding the biology of the microbiome is a starting point for considering its relationship to asthma. There are seven critical characteristics. First, the human microbiome is niche-specific. In each anatomical locale that harbors a microbiome, the microbial populations differ. These populations are both unique and overlapping, and there is evidence for interactions between them.[2] Even niches that once were considered to be 'sterile,' are being shown to contain resident microbial populations, including the esophagus, stomach, and lower respiratory tract.[3] Second, in all niches, there are both persistent and transient organisms; although the definitions and boundaries vary, and are biologically relevant, the emphasis of investigation has been on understanding the persistent microbiota-the organisms that may endure for years, decades, or life.

Third, across individuals, the microbiota are taxonomically highly diverse. This diversity has been best studied in relation to bacterial populations, but also is present for fungi and viruses. At a functional level, the overall outlines are more conserved, since, for example, all bacteria use stereotypic mechanisms to process energy, build cell walls, reproduce, and move, but nevertheless there is enormous variation as well. Fourth, the microbiota in aggregate are numerous. Current estimates are that the number of bacterial and human cells in our bodies are roughly equivalent with residential viruses perhaps ten-fold greater. At a genetic level, the differences are greater. In comparison to the current view of 23,000 human genes, each of us carries from 2-20 million unique bacterial genes, all subject to regulatory pathways.[2]

Five, the microbiome is ancient. All animals have their own characteristic microbiomes. Among vertebrates, the phylogenies of the microbiota parallel those of their hosts. This provides strong evidence for the overall vertical transmission of the microbiome and also supports the concept of co-evolution of host and microbial population.[4] In studies of primates, the congruent phylogenies, at the aggregate level, and for particular marker taxa, is consistent with the overall view, and provides a milestone of at least 8 million years of congruence.[5] Sixth, the essential structure of the microbiome is acquired early in life. In the womb, human life begins in a mostly sterile environment; there is no reproducible evidence for an in utero persistent microbiome. Exposure to microbes begins when the water breaks, the first step in the introduction and transfer of maternal microbiota to the infant. There are multiple parallel and redundant routes involving colonizing the gastrointestinal tract, mouth, and skin. The population structure of the infantile microbiome develops gradually and progressively, and by the age of three, in the GI tract at least, has taken on the major characteristics of the adult microbiota.[6]

Seven, the microbiota is interactive with host physiology. Studies focusing on immunity, metabolism, and cognition all provide evidence for strong microbiota effects on all these characteristics, with reciprocal properties as well.[7, 8] It is this property, in the context of the above characteristics, that require attention in relation to asthma and allergic disorders.

3. The human microbiome is changing.

With the advancements in economic and social development over the past two centuries have come new pressures on the human microbiome, accelerating in the past 50 years. Clean water, with all of its important benefits, limits the interpersonal spread of commensal organisms. Cesarean sections, now occurring in more than half of pregnancies in some populations, and 25-33% in many others, bypasses the original microbial seeding that occurs during natural delivery. Formula feeding, substituting for human breast milk, does not contain the micronutrients that evolved over the eons to nourish ancestral microbes. The use of anti-bacterial agents in foods, and in topical applications impacts the developing microbiome. Most importantly, human children all over the world are receiving multiple courses of potent antibiotics, often at high dose, over the early years of life. All of these practices have been predicted to affect microbial composition and thus host physiology.[9, 10] Based on the largely vertical transmission of the microbiota, it was predicted that that loss of diversity would be cumulative across human generations.[11]

Unfortunately, there is increasing evidence that these predictions were correct. Studies of human populations at differing levels of socio-economic advancement have shown the highest microbiota diversity in populations with limited access to modernization and lowest diversity in peoples in industrialized countries.[12, 13] These trends are irrespective of continent of origin, diet, and ethnicity, but point to modernization/urbanization and all of its accompanying trends as the key factor. Recent studies of immigrants to the USA from developing countries provide evidence of loss of diversity in real time.[14]

These trends have been encapsulated in the *Theory of the Disappearing Microbiota*[9, 10] which has two major tenets: (i), changed human ecology has altered transmission and maintenance of

ancestral microbes, which affects the composition of the microbiota, and (ii), the microbes, both good and bad, usually acquired *early in life* are especially important, since they affect a developmentally critical stage. Since the interaction of the microbiota with human physiology is so profound, this theory predicts that the changed microbiota affects host physiological functions,[15] with immunity being particularly relevant to asthma. Although the potential for antibiotics to lead to important ecological effects has been well-recognized, most of the focus has been on the development of antibiotic resistance. Although resistance is quite important, it probably represents only the tip of the iceberg (**Figure 1**), in which the larger mass, currently hidden from plain view is the effects on microbiome composition and the subsequent physiological and clinical consequences. These views concern exposure to and acquisition of human-specific ancestral microbiota, and can be contrasted with a more general construct, "the hygiene hypothesis," which largely focuses on environmental exposures, including to domesticated animals.[16]

4. *Helicobacter pylori* as an indicator organism and protagonist.

Initially identified in the 19th century, the organisms that now are called *Helicobacter pylori* were first isolated from human gastric biopsies in 1983.[17] There is considerable evidence that *H. pylori* is ancient,[18] having colonized our ancestors at least 100,000 years ago.[19] Based on its ancientness, its presence in all human populations in which it has been studied, its acquisition in early life and life-long persistence*, H. pylori* clearly can be considered as a member of the human gastric microbiota, and when present is usually the dominant member of the gastric microbiota.[20] However, it is progressively disappearing from human populations, reflecting many of the trends mentioned above. As such, it is possible to associate its presence or absence with human diseases. First discovered as a pathogen in the 1980's, the presence of *H. pylori* is clearly linked to the risk of developing peptic ulcer disease and adenocarcinoma of the stomach.[21] However, its absence has been linked to esophageal diseases including Gastro-esophageal Reflux Disease (GERD), Barrett's Esophagus, and adenocarcinoma of the esophagus and the adjacent G-E junction.[22] Similarly, its absence has been linked in multiple large, blinded, epidemiological studies, with the risk of developing childhood-onset asthma.[23-25] *H. pylori* strains may be divided into those possessing the *cag* island with host-interactive genes or not.[26] The *cag*+ strains are those that are most strongly related to risk of disease (ulcers and cancer) as well as protection from disease (esophageal diseases, asthma), which is consistent, since this is the subset of strains with the strongest host interactions.[26] The epidemiologic studies also found parallel relationships with hay fever and cutaneous allergies, two disorders independently linked with asthma.[23] Results of these epidemiologic studies generate the hypothesis that gastric *H. pylori* colonization is protective against asthma and related disorders, and that the rise of asthma is at least in part fueled by the loss of this ancestral gastric colonizer, with loss of protective immunological functions (to be discussed below).

5. Role of the microbiome in immune development (evidence in humans and in model systems.

The microbiota is a known regulator of immune development, cell differentiation, and cell function. Increasing evidence over the past decade has shown that specific bacterial strains as well as defined mixtures of bacteria can elicit predicted immune phenotypes.[8, 27-29]

Intestinal

Specific members of the murine microbiome, some of which are shared with humans, have stereotypical interactions with immunological effector cells. Specific clades of clostridia species isolated from human stool samples can induce colonic T regulatory cells (Tregs) in a murine model.[27] Segmented filamentous bacteria (SFB; Candidatus *Savagella*) are members of murine microbiota that elicit Th17 differentiation in the intestinal tract of mice.[28] *Helicobacter hepaticus* induce RORgt$^+$ T regulatory cells that suppress Th17 cell function; in the absence of these induced Tregs, *H. hepaticus* potentiates Th17-driven colitis.[30] A mixture of 11 human commensal bacterial strains has been identified that induced IFNg production by CD8$^+$ T cells in the mouse colon; these had effector functions useful in anti-pathogen and anti-tumor responses.[29] The above taxa provide examples of how well-characterized bacterial commensals can drive immune differentiation and translate to actionable phenotypes within the intestinal environment.

Gastric

H. pylori, an ancient, persistent and vertically transmitted constituent of the gastric microbiota, is among the best studied examples of a highly immunomodulatory bacterium with potent effects on asthma risk and severity. Not only do large epidemiological studies point to an inverse association of *H. pylori* with allergic asthma, especially in children and young adults;[11, 24, 25, 31] there also is substantial experimental data from mouse models to provide evidence for causality. The gold standard mouse models of allergen-induced airway inflammation and hyper-responsiveness entail the sensitization, and subsequent challenge (both ideally performed intranasally or intratracheally to mimic the dominant route of exposure in humans) of mice with potent allergens such as ovalbumin or house dust mite extract. In such experimental models, chronic infection with *H. pylori* efficiently reduces the markers of allergic asthma including: (i), excessive pulmonary Th2 responses and associated high levels of the Th2 cytokines IL-5 and IL-13; (ii), aberrantly high systemic levels of allergen-specific IgE; [32], bronchoalveolar eosinophilia; and (iv), goblet cell hyperplasia and the associated excessive mucus production.[33] Lung function is restored as well in *H. pylori*-infected mice as determined by methacholine challenge assay.[33] In line with observations in humans, which highlighted particularly strong inverse associations of *H. pylori* with early-onset asthma,[11, 31] the experimental data suggest that neonatal infection with *H. pylori*, but not infection of adult mice, results in protection against allergic asthma signs and severity.[33] Several prerequisites of protection have been identified in addition to the early-life window of opportunity, which may be considered as the "neonatal tolerance window".[34, 35] In particular, an immunomodulatory molecule that all *H. pylori* strains produce, the so-called vacuolating cytotoxin, has been implicated in *H. pylori*'s asthma-protective effects.[36-38] VacA-deficient isogenic mutants fail to protect against allergic asthma in neonatal infection models,[38] and VacA purified from culture supernatants of *H. pylori* is very potent at suppressing allergic asthma in prophylactic settings.[37] More recent tracing experiments have shown that VacA targets different myeloid cells in the gastric mucosa, generating a tolerogenic environment characterized by high levels of immunoregulatory cytokines such as IL-10 and TGF-ß (**Figure 2**).[36] As VacA is not only required for the protective effects of live infection, but sufficient to prevent allergy on its own, it deserves to be investigated further and developed for possible interventional application in humans.

H. pylori has not only been inversely linked to allergic asthma, but also appears to have strong immunomodulatory and beneficial effects in other settings of allergic and chronic inflammatory, and possibly autoimmune disorders. In particular, patients with either of the two major forms of inflammatory bowel disease, Crohn's disease and ulcerative colitis, harbor *H. pylori* at much lower rates than the general population.[39] In mouse models of IBD, *H. pylori* infection and regular administration of *H. pylori* extracts protects against severe disease as determined by histological analysis, and other readouts.[40] Among allergic disorders, food allergy to ovalbumin allergen and peanut extract has been shown to be alleviated by live *H. pylori*, its extract as well as purified VacA.[41] One study has shown an inverse association of *H. pylori* infection with multiple sclerosis, and has provided experimental evidence in the mouse model of MS, experimental autoimmune encephalomyelitis (EAE), for protective effects of *H. pylori* on the CNS findings associated with this disease.[42] Atopic dermatitis is another allergic disease manifestation with which *H. pylori* has been inversely linked in humans,[43, 44] as well as skin sensitivity to a panel of allergens[22], but experimental data to support protective effects of the bacteria in the skin are not available. In yet another study, the presence of *H. pylori*, was inversely related to the diagnosis of celiac disease.[45] but the direction of causality has not been confirmed.

H. pylori creates a tolerogenic environment in the gastric mucosa that is at least in part driven by VacA and its interactions with the myeloid compartment.[46] Recent work has shown *H. pylori* (expressing RFP, and thereby allowing its tracking to specific immune compartments) to interact directly with various myeloid cell populations, which are recruited to the gastric mucosa along chemokine gradients.[46] At least six distinct myeloid populations with diverse functions appear in the mouse stomach upon *H. pylori* infection, but are virtually absent in the steady state stomach;[46] of these, three are considered *bona fide* dendritic cells (DCs), as they express CD11c and depend on the growth factor FLT3 ligand for their differentiation from bone marrow precursors. The others are macrophages and monocytes expressing the respective lineage markers F4/80, CD64 and Ly6C, among others. RFP^+ bacteria are in direct contact with all macrophage and monocyte, and some, but not all, DC lineages in the gastric lamina propria, and also encounter large numbers of eosinophils in their natural environment.[46, 47] Some of these interactions have been investigated functionally using mouse strains deficient for the respective lineages. From this work, it is now clear that $CD103^+$ DCs are required for Th1-driven immunity on the one hand, and for the recruitment to infected tissues of peripherally induced Tregs (pTregs) on the other.[48] In the absence of $CD103^+$ DCs (in $BATF3^{-/-}$ mice, which lack the key transcription factor driving $CD103^+$ DC differentiation[49]), the priming of Th1 cells and pTregs in lymph nodes proceeds normally, but both T-cell subsets fail to upregulate expression of the chemokine receptor CXCR3, and therefore cannot traffic to the infected gastric mucosa along CXCL9 and CXCL10 chemokine gradients (**Figure 2**).[48] The defects of $BATF3^{-/-}$ mice in both populations manifest in two ways: on the one hand, $BATF3^{-/-}$ mice are severely hypercolonized since they cannot control *H. pylori*[48] and on the other hand, they are not protected against allergic asthma upon neonatal infection due to their functional Treg defect.[37]

Another cell type that is emerging as playing a critical role at the interface of *H. pylori* with its host is the eosinophil, a cell type that has mostly been associated with Th2-driven immune responses to parasites and allergens. Eosinophils, as with other myeloid populations, are recruited to the *H. pylori*-infected gastric mucosa in large numbers and come in direct contact

with live bacteria. This interaction does not result in *H. pylori* killing, despite the fact that eosinophils have potent bactericidal activity towards other gastrointestinal pathogens, such as *Citrobacter rodentium*.[47] Rather, it appears as if eosinophils acquire immunoregulatory activity in the gastrointestinal lamina propria, at steady state and during infection, and suppress inappropriate or excessive Th1 responses to promote tissue homeostasis and control inflammation. Indeed, eosinophil-deficient mice control *H. pylori* more efficiently than their eosinophil-proficient counterpart, which has been attributed to their unrestricted Th1 responses.[47]

Several studies in humans and mice have pointed to the relative strength of effector T-cell and Treg responses to *H. pylori* infection as a major determinant of disease risk and severity, both with in the stomach and outside. Humans with a Treg-predominant anti-*H. pylori* response are less likely to develop gastric ulcers than those with a Th1 or Th2 polarized effector T-cell response to the organism, and the levels of circulating *H. pylori*-specific Tregs, especially those producing the regulatory cytokine IL-10, are inversely associated with serum IgE levels.[42, 50, 51] In *H. pylori*-infected children, gastritis manifestations are typically much less severe than in adults, and effectively controlled by a dominant Treg response.[52] These data are all in line with beneficial effects of *H. pylori* in childhood and adolescence, but not later in life, and implicate *H. pylori*-specific Tregs as mediators of asthma protection. Several lines of experimental evidence from mouse models support this idea: (i), neonatally infected mice develop much less severe gastritis upon *H. pylori* infection than mice exposed as adults, and never exhibit evidence of preneoplastic lesions, which are common in adult-infected animals[53] ; (ii), in asthma models, protection is limited to mice infected as neonates[33] ; and [32], depletion of Tregs abrogates protection in the neonatal infection model, and the adoptive transfer of $Foxp3^+$ Tregs is sufficient to confer protection in naïve recipients.[33] The protective population of Tregs has yet to be characterized in detail using functional approaches, but appears to be pTregs rather than thymus-derived, and expresses the transcription factors ROR□t and Tbet.[36, 48] *H. pylori*-induced pTregs are enriched in the infected mouse gastric mucosa, but traffic to and accumulate in the lungs (**Figure 2**). This (mis) localization is specific to neonatally infected mice and believed to underlie the protective effects of neonatal infection on pulmonary manifestations of allergic diseases.[36, 48] In another murine model with experimental *H. pylori* challenge, colonization led to changes in gastric gene expression, immunological function and hormone secretion, and effects on the intestinal microbiota, as well as changes in pulmonary gene expression and T-cell populations, supporting the linkage with extra-gastric pathophysiology.[54]

Skin

Applied to the skin of mice, human cutaneous commensals elicited both cytokine and T cell responses; of those, *Staphylococcus epidermis* was unique in its ability to induce CD8 T cells producing IL17 at the inoculation site.[55] Commensal-specific T cells, both $CD4^+$ Th17 and $CD8^+$ Tc17 cells, are transcriptionally programmed to maintain a Type 17 anti-microbial response and a Type 2-poised response that is elicited in response to tissue inflammation, epithelial damage, and alarmins.[56] This work identifies how microbiota-driven immune development plays a role in maintaining physiological homeostasis and adaptable immune responses at mucosal sites.

Age, microbiota, and immunity

There is strong evidence that the age of the host is an important factor contributing to the host-immune axis. An important concept is that there is a critical window of development in which

the microbiota regulate the immune education that cannot be meaningfully altered once that time period has elapsed.[57] (**Figure 3**). The acquisition of host-specific microbiota at birth differentially regulates intestinal immunity; mice raised with murine microbiota were more protected against gastrointestinal pathogens than mice raised with human microbiota.[58] Several lines of evidence support the view that the composition of the microbiota during early-life plays a critical role in immune phenotypes observed later in life. The maternal microbiota also plays a role in regulation of the offspring's innate immunity,[59] indicating that such development starts *in utero* and further points to post-natal events that regulate the immune maturation. In an animal model, age at the time of first exposure is a major determinant of the outcome of the *H. pylori*/host interaction. Whereas the neonatal tolerance window closes at 7-10 days after birth in mice, it may commence well before delivery. Evidence towards this end comes from studies in which mice were exposed to *H. pylori* extract *in utero* or transmaternally during lactation.[41] Such offspring showed substantial protection against allergic disease manifestations, independent of the protection status of the mother.[41]

These concepts support the importance of further characterizing early-life host-microbiota interactions, and going forward require focus on interventions that may have lasting clinical benefits.

6. The microbiome as a mediator of asthmatic disease

There also is evidence to support a role for both exogenous and endogenous microbiota contributing to childhood asthma development. For example, prenatal exposure to a rural farm environment correlated with protection against atopic sensitization in children.[60] In large epidemiological studies, antibiotic use during the first year of an infant's life correlated with increased asthma risk in young children.[61, 62] Similarly, in British Columbia, a period of decreased antibiotic use during the first year of life significantly correlated with reduced asthma risk. [63] There is sufficient evidence to support that antibiotic use, mode of delivery, and diet can impact composition of the human infant microbiota.[64] In support of the importance of microbial exposure and susceptibility to asthma, low doses of endotoxin were protective in a murine model of house dust mite-induced airway inflammation[65]; in the same model, germ free mice had stronger immune responses.[66] Germ-free mice have higher serum IgE levels than select pathogen free (SPF) mice. As such, germ-free mice having increased susceptibility to anaphylaxis, a phenotype that can be ablated when mice are inoculated with a diverse microbiota before 6 weeks of age.[67] Collectively such evidence indicates that overall, increased exposure to certain types of bacteria or their products during early life correlates with protection from asthma and allergic diseases.

In the CHILD cohort in Canada, children at risk for asthma were found to have reduced abundance of the genera *Lachnospira*, *Veillonella*, *Faecalibacterium*, and *Rothia*, as well as reduced fecal acetate levels. Transfer of fecal samples from at-risk children to germ-free mice, and restoring the missing bacterial genera, reduced the asthma phenotypes in an ovalbumin model of airway inflammation.[68] In a Danish prospective cohort study on asthma, an association between the human fecal microbiota composition at 1 year and asthma risk at age 5 was identified. Specifically, children born to asthmatic mothers and displaying altered microbial composition at age 1 were 13-times more likely to have asthma at age 5 than other children in the

cohort.[69] In the US, children at the highest relative risk of atopy and asthma had reduced abundance of *Bifidobacterium*, *Akkermansia*, and *Faecalibacterium* in the neonatal gut, and enrichment of the linoleic acid 12,13-diHOME, a bacterial metabolite.[70] In a murine asthma model, increasing intestinal concentrations of 12,13-diHOME led to reduced pulmonary Treg abundances and increased inflammation.[71] Overall, these studies have identified important and overlapping evidence of particular bacterial genera and metabolites that correlate with protection from asthma.

Beyond the gastrointestinal tract, the human lung bacterial community appears to be dominated by 6 genera during the first two years of life, at which point further diversification takes place. Colonization with pathogens predicts chronic wheeze in sensitized children. In addition, children with increased abundance of *Streptococcus*, *Hemophilus*, and *Moraxella* in induced sputum samples had increased risk of chronic wheeze at age 5.[72] Asthmatic patients were also reported to have increased diversity in the lung microbiota, but reduced biomass.[73] These findings support roles of the pulmonary microbiota in influencing susceptibility to asthma, in addition to the influence of the gastrointestinal tract microbiota on asthmatic pathophysiology

7. Solutions

Based on the increasing evidence of microbiota roles in asthma, it is important to begin to consider specific solutions to both prevention and treatment. An obvious approach, which nevertheless must be stated, is to avoid further damage to the microbiome. Physicians and parents should juxtapose the physiological costs of antibiotic courses, formula feeding, and Cesarean section when considering their benefits in individual patients. A more accurate estimation of antibiotic benefit and risk would clearly reduce their overuse, as well as that for other medical interactions. The conversation should shift from “this might be helpful,” to “is this necessary?’

A more specific approach is to attempt to restore particular disappeared organisms to either prevent or treat asthma. The development of such approaches will ultimately require clinical trials to assess benefit and risk. All over the world, patients with asthma are taking ‘probiotics’ that can be bought over the counter or prescribed by their physician. The actual base of scientific knowledge that underpins the use of these diverse products in millions of individuals is surprisingly sparse. As above, clinical trials are needed to test their efficacy. An intriguing possibility will be to give *H. pylori* to children to restore this ancestral organism (**Figure 4**) and take advantage of its asthma- and reflux-reducing properties, and then eliminate it with antibiotics in adulthood to reduce its potential to drive gastric cancer. Clinical trials now aim to also exploit the prenatal window of opportunity. In one trial, pregnant women and prospective mothers of at-risk offspring are being given the prebiotic inulin, to determine effects on the occurrence of atopic dermatitis as a primary end-point and early predictive readout of allergy.[74] A recent meta-analysis of 28 studies investigating the effects of probiotics given pre- and/or post-natally concluded that the risk of atopic dermatitis (as the earliest possible readout of atopy) could be reduced by starting probiotic treatment during gestation and continuing it through the first six months of the infant's life.[75] The available mouse data suggest that live *H. pylori*, or its

extract, might be equally or more efficient than pre- or probiotics at reducing allergy risk when given as early as possible in life.

In the future, microbes that have stereotypic interactions with particular arms of human immunity will be important candidates for trials. Alternatively, microbes or chemicals (prebiotics) that have no direct effect in immunity, but which nourish or stabilize endogenous immunologically active populations, may be useful. Recent studies that have identified particular taxa[68, 69] and bacterial metabolites[70] associated with reduced asthma risk in human children may be especially useful.

If the most beneficial organisms for asthma prevention have already largely disappeared from developed country populations, where will we obtain the organisms necessary for restoration? One solution will be to identify individuals and populations with little or no exposure to the modernizing practices, and stockpile these specimens and purified cultures for future generations. A non-governmental non-profit foundation has recently been established [The Microbiota Vault, Inc.: microbiotavault.org] **(Figure 5**) to facilitate this process,[76] in analogy to the Seed Vault, now in existence to preserve our precious patrimony of seeds for food cultivation.

8. Conclusions

A growing body of evidence is linking the microbiome—respiratory and gastro-intestinal—with the altered pathophysiology operant in asthma and related allergic disorders. Such linkage is biologically plausible, and ultimately actionable, since tools already are in existence to reshape the microbiome in desired directions. However, much foundational work must be done to establish particular preventive and therapeutic modalities. Nevertheless, the promise is great for curtailing the pandemic of asthma by applying the knowledge learned about microbiome-immunologic interactions. Further explorations in this clinically important area will deepen our understanding of human immunology as well, with applications to other immune and auto-immune conditions.

What do we know?

- We know candidate organisms identified in both the gastric mucosa (*H. pylori*) and intestinal tract that can confer protection in murine asthma models and correlates with protection in humans
- We have begun to identify bacterial lung species, intestinal species, and metabolites that correlate with asthma or atopy.

What do we still need to know?

- We need to better understand how to take actionable steps to modulate the microbiota, and the windows of time at which these interventions are optimal in human hosts.
- We need a greater understanding of how candidate strains of bacteria or their metabolites interact with the rest of the microbiome. In the context of an ecosystem, we need to understand how one introduced member impacts the whole.

- Although there is a growing body of evidence with respect to metabolites and bacterial strains on T regulatory cells in asthmatic disease, we need to further advance our understanding of how bacteria-driven immune differentiation can alter immune responses to environmental antigens and allergens.

Figure legends

Figure 1. Ecological effects of antibiotic exposures. Antibiotic resistance has long been recognized as an ecological consequence of antibiotic exposure. However, an additional hypothesis is that, like the proverbial iceberg, the disruption of the microbiome leading to clinical consequences, is the 'inapparent' or larger part'. Even transient antibiotic exposures, in early life or prior to adventitious infections, can lead to long-term consequences.[61, 64, 77, 78] Exposures of women before the birth of their children can lead to consequences in the next generation,[61] and exposures of adults can enhance risk of both metabolic and neoplastic diseases.[79]

Figure 2. *Helicobacter pylori* infection is strictly local but has systemic effects at distant sites. Half of the world's population carries *Helicobacter pylori*; in endemic regions with high (>80% prevalence), *H. pylori* transmission occurs within the first two years of life, and mostly from mother to offspring. The only reservoir of live *H. pylori* is the human stomach; it is not found in other tissues of the body or in the stomach in other species. *H. pylori* either swims freely in gastric mucus or binds to gastric epithelial cells. In experimental models, the bacteria recruit cells of myeloid origin into the gastric lamina propria, which are known to interact with live bacteria or their products, presumably through intraepithelial protrusions. VacA and the enzyme g-glutamyl-transpeptidase (GGT) are two immunomodulators that all *H. pylori* strains express and use to manipulate myeloid cells. Antigen-presenting cells, and in particular $CD103^+$ DCs, migrate to the draining gastric and mesenteric lymph nodes, where they prime T-effector (mostly Th1 and Th17) and regulatory T-cell (Treg) responses. *H. pylori*-induced Th1 cells and Tregs substantially express the chemokine receptor CXCR3 on their surface, which allows for their trafficking to the stomach along a gradient of the CXCR3 ligands CXCL9 and 10. In the absence of $CD103^+$ DCs, this trafficking does not happen and mice are hypercolonized. The Treg population that changes most with *H. pylori* colonization are peripherally induced Tregs (pTregs), distinguishable from their thymus-derived counterparts by their RORgt and Tbet, and lack of neuropilin expression. pTregs in the gastric mucosa suppress pathogen-specific Th1 responses and promote persistent *H. pylori* colonization. Importantly, pTregs with the same profile also traffic to, and accumulate in, the lungs of infected mice, where they likely are involved in the suppression of allergen-specific Th2 and Th17 responses; pTregs strongly produce TGF-ß and IL-10.

Figure 3. Early life influences on the developing microbiome affect 'immunological tone'. The maternal microbiome interacts with the mother's immune system, which then further shapes the microbiome; it is a continuous cycle. At birth, the maternal microbiome is transferred to the baby as well as immunological molecules (including antibodies, cytokines, and specific metabolites). Together, these interact with innate immunity to set 'immunological tone,' which

then affects the development of adaptive immunity. Many aspects of modern health care can perturb these relationships.

Figure 4. A prediction for the medicine of the future. For well-baby visits, future pediatricians will examine both babies and their diapers. They will determine whether that infant has the ideal microbiota for their genotype and other markers. If not, they will administer the 'missing microbes' to optimize their health trajectory through life. Physicians will follow microbiological parameters during childhood, adjusting as necessary, to continue optimization.

Figure 5. Creating a repository to preserve the ancestral microbiota. A non-profit foundation (The Microbiota Vault, Inc.; *www.microbiotavault.org*), has been established to develop a global repository that can be used to facilitate microbiome restoration in future generations.[76]

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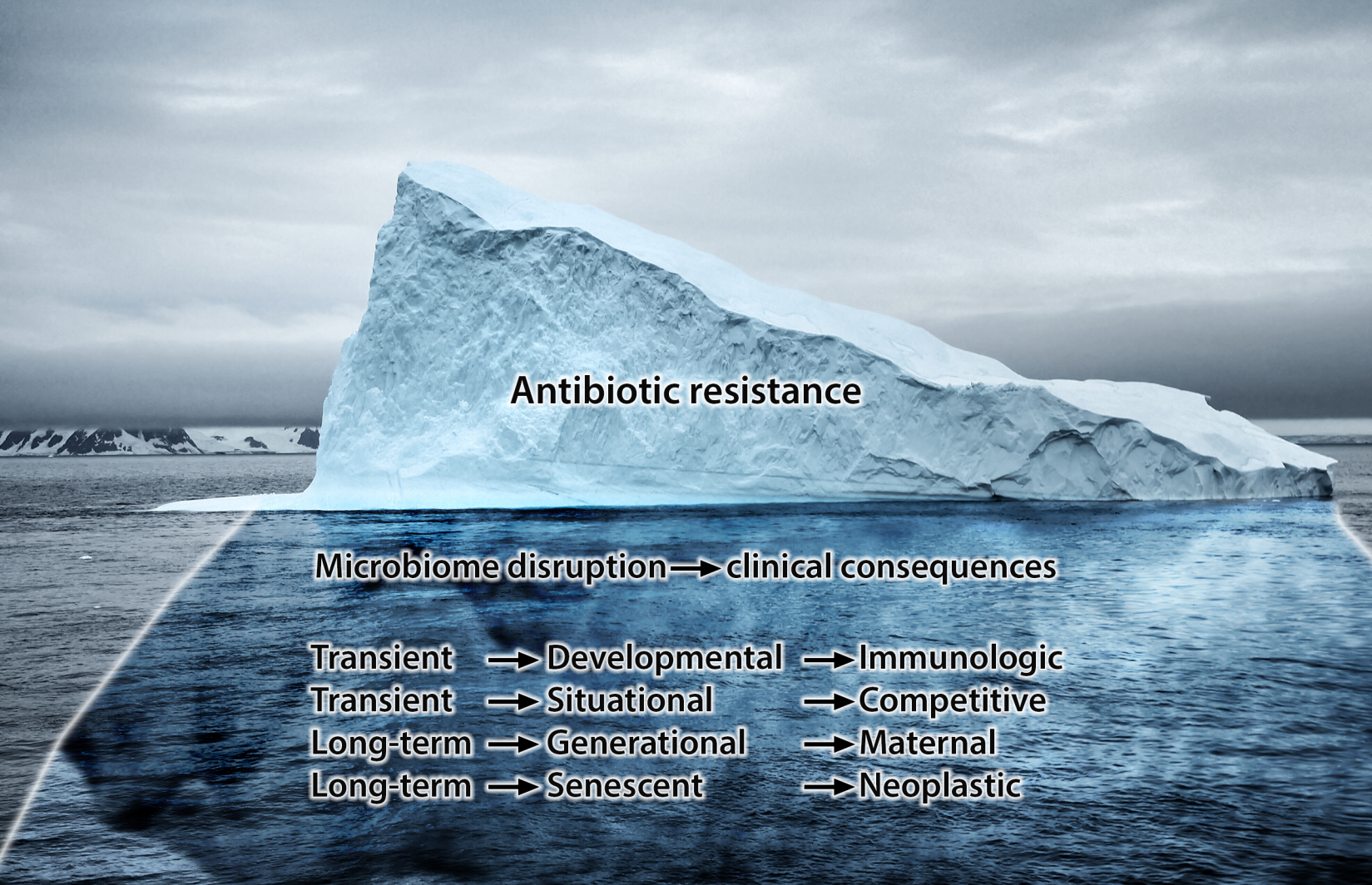
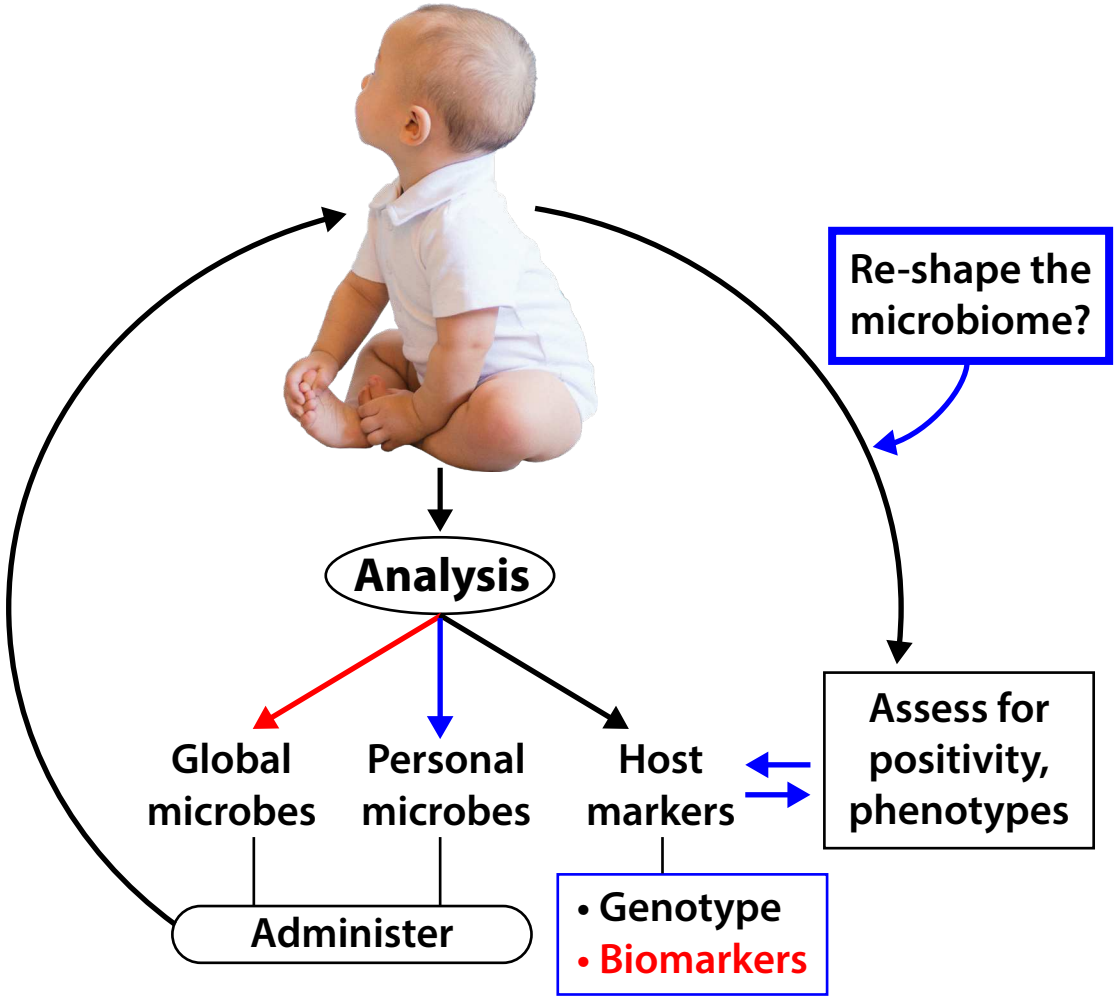
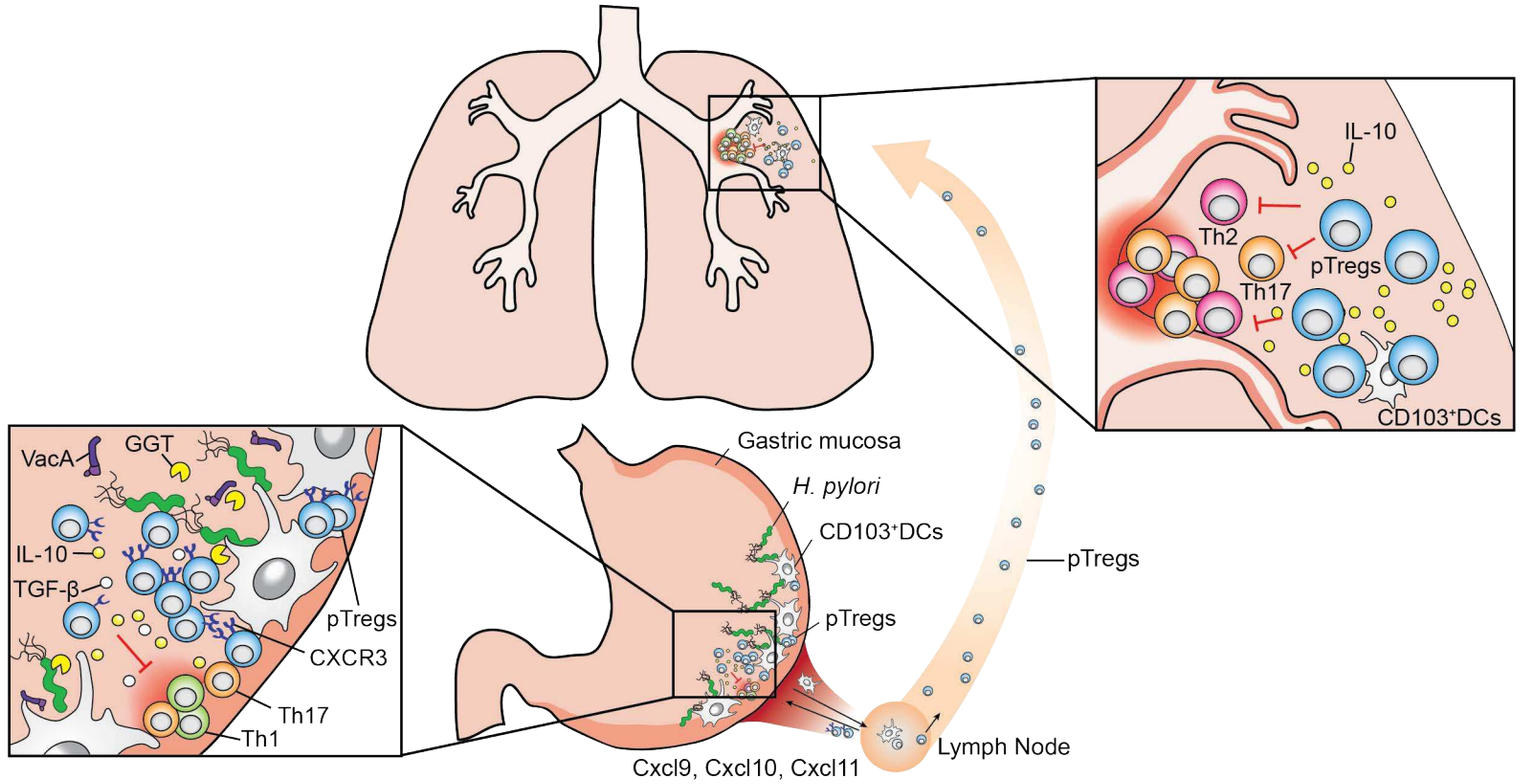

Antibiotic resistance
Microbiome disruption → clinical consequences
Transient → Developmental → Immunologic
Transient → Situational → Competitive
Long-term → Generational → Maternal
Long-term → Senescent → Neoplastic


Re-shape the microbiome?
Analysis
Global microbes
Personal microbes
Host markers
Assess for positivity, phenotypes
Administer
• Genotype
• Biomarkers

The Microbiota Vault

A global non-profit effort to conserve long-term health for humanity


IL-10
Th2
pTregs
Th17
CD103⁺DCs
Gastric mucosa
H. pylori
CD103⁺DCs
pTregs
pTregs
pTregs
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Cxcl9, Cxcl10, Cxcl11
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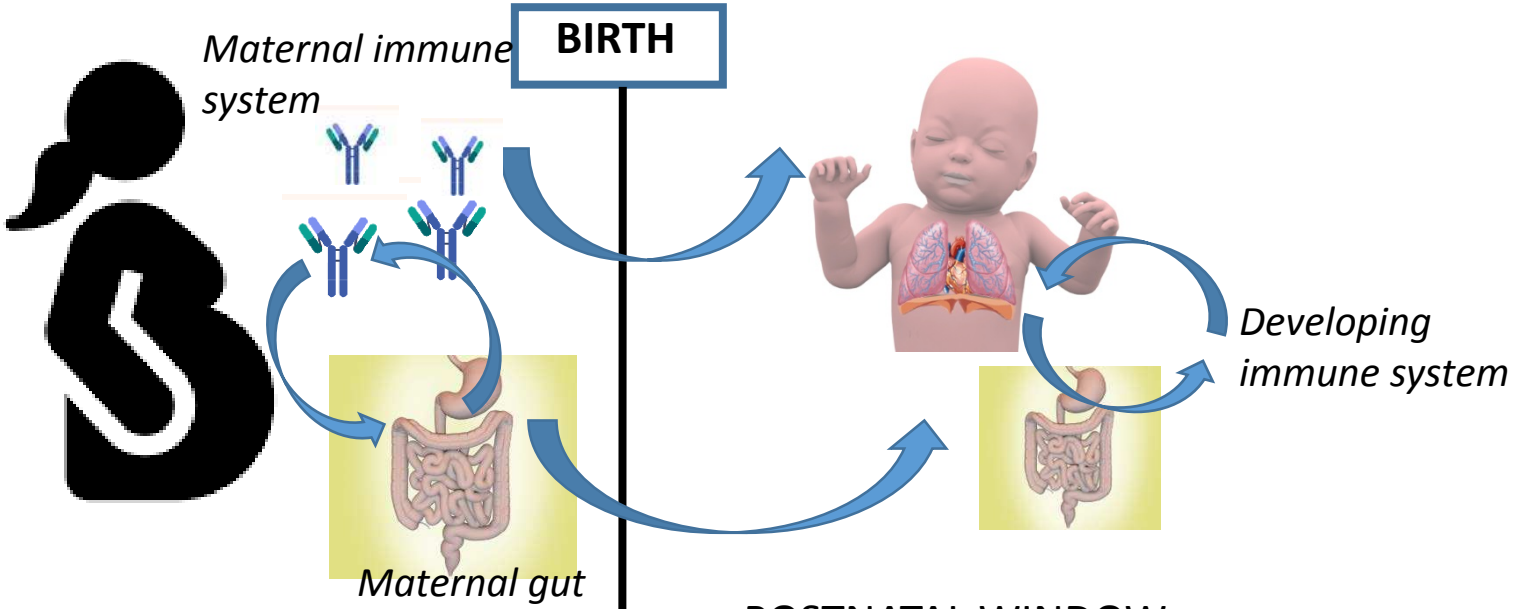
GGT
IL-10
TGF-β
pTregs
CXCR3
Th17
Th1



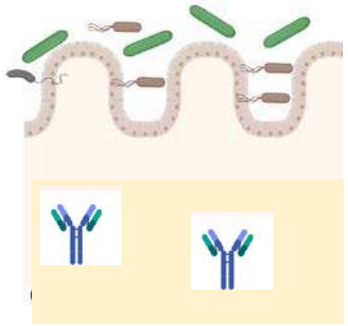
PRENATAL WINDOW

- Maternal antibiotics
- Environmental exposure
- Maternal immune state

POSTNATAL WINDOW

- Maternal influences
- Environment
- Infant antibiotic use
- Microbiota diversity acquisition

EARLY LIFE MICROBIOTA



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Innate immunity priming, differentiation, education

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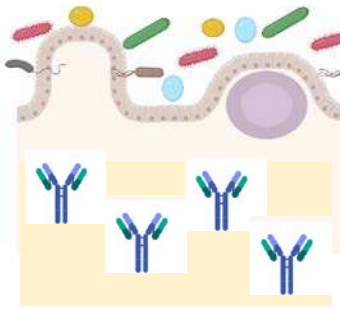

Innate Development impacts future Adaptive immune development and responses